

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07H 19/167, A61K 31/70	A2	(11) International Publication Number: WO 98/08855
		(43) International Publication Date: 5 March 1998 (05.03.98)

(21) International Application Number: **PCT/US97/14724**(22) International Filing Date: **20 August 1997 (20.08.97)**(30) Priority Data:
08/702,234 **27 August 1996 (27.08.96)** **US**(71) Applicant (for all designated States except US): **CV THERAPEUTICS, INC. [US/US]; 3172 Porter Drive, Palo Alto, CA 94304 (US).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LUM, Robert, T. [US/US]; 781 Barron Avenue, Palo Alto, CA 94306 (US). PFISTER, Jurg, R. [US/US]; 1500 Oak Steet, Los Altos, CA 94024 (US). SCHOW, Steven, R. [US/US]; 204 Mendocino Way, Redwood City, CA 94065 (US). WICK, Michael, M. [US/US]; 16 Beresford Road, Chestnut Hill, MA 02146 (US). NELSON, Marek, G. [US/US]; 2690 Park Way, Sunol, CA 95051 (US). SCHREINER, George, F. [US/US]; 12774 Leander Drive, Los Altos Hills, CA 94022 (US).**(74) Agent: **HUGHES, A., Blair, McDonnell, Boehnen, Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).**(81) Designated States: **AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).**

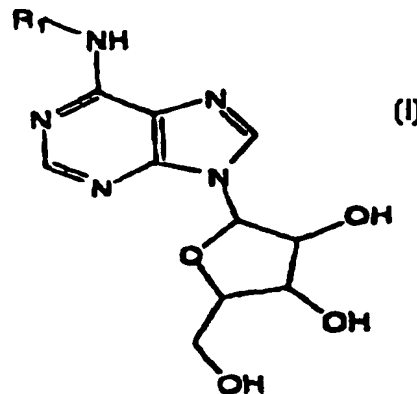
Published

Without international search report and to be republished upon receipt of that report.

(54) Title: **N⁶ HETEROCYCLIC SUBSTITUTED ADENOSINE DERIVATIVES**

(57) Abstract

A substituted N⁶-oxa, thia, thioxa and azacycloalkyl substituted adenosine derivative of formula (I) and a method for using the composition as an A₁ heart adenosine receptor. In said formula, R₁ is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 atoms, at least one of which is selected from the group consisting of N, O, P and S-(O)₀₋₂ and wherein R₁ does not contain an epoxide group.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

**TITLE: N^o HETEROCYCLIC SUBSTITUTED
ADENOSINE DERIVATIVES**

BACKGROUND OF THE INVENTION

Field of Invention

10 This invention encompasses optimally substituted N^o-oxa, thia, thioxa and azacycloalkyl substituted adenosine derivatives that are selective adenosine type 1 receptor agonists, and as such, are potentially useful agents for the treatment cardiovascular diseases and central nervous system disorders.

Description of the Art

15 There are two subtypes of adenosine receptors in the heart: A₁ and A₂. Each subtype effects different physiological functions. Stimulation of the A₁ adenosine receptor induces two distinct physiological responses. The first is the inhibition of the stimulatory effects of catecholamine. This effect is mediated via the inhibition of cyclic AMP synthesis. The
20 second effect mediated by A₁ receptors is the slowing of the heart rate and impulse propagation through the AV node. The effect is independent of cAMP metabolism and is associated with A₁ adenosine receptor activation of the inwardly rectifying K⁺ channel. This effect is unique to the A₁ receptor; there is no role for the A₂ receptor in modulating the function of this channel. Stimulation of the adenosine A₁ receptor accordingly shortens the
25 duration and decreases the amplitude of the action potential of AV nodal cells and subsequently prolongs the refractory period of the cells. The consequence of these effects

is to limit the number of impulses conducted from the atria to the ventricles. This forms the basis of the clinical utility of A₁ receptor agonists for the treatment of supraventricular tachycardias, including atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia.

5 The clinical utility of A₁ agonists therefore would be in the treatment of acute and chronic disorders of heart rhythm, especially those diseases characterized by rapid heart rate where the rate is driven by abnormalities in the atria. The disorders include but are not limited to atrial fibrillation, supra ventricular tachycardia and atrial flutter. Exposure to A₁ agonists causes a reduction in the heart rate and a regularization of the abnormal rhythm
10 thereby restoring improved hemodynamic blood flow.

A₁ agonists, through their ability to inhibit the catecholamine induced increase in cAMP, should have beneficial effects in the failing heart where increased sympathetic tone causing enhanced cAMP has been associated with increased likelihood of ventricular arrhythmias and sudden death.

SUMMARY OF THE INVENTION

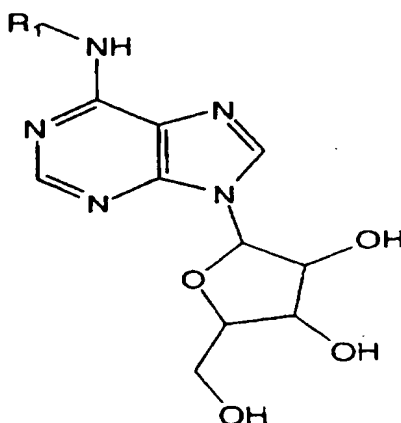
An object of this invention is novel heterocyclic substituted adenosine derivatives.

Another object of this invention is novel heterocyclic substituted adenosine derivatives that are useful as A₁ receptor agonists.

5 Still another object of this invention is novel heterocyclic substituted adenosine derivatives that are useful for treating supraventricular tachycardias, including atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia.

In one embodiment, this invention is a composition of matter having the formula:

10



15

wherein R₁ is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 atoms, at least one of which is N, O, S, P and wherein R₁ may be mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower
20 alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof wherein R₁ does not contain an epoxide group.

In another embodiment, this invention is a method for stimulating coronary activity in a mammal experiencing a coronary electrical disorder that can be treated by stimulating an A₁

heart adenosine receptor by administering a therapeutically effective amount of the composition disclosed above to the mammal.

In still another embodiment, this invention is a pharmaceutical composition of matter comprising the composition of this invention and one or more pharmaceutical excipients.

DESCRIPTION OF THE FIGURES

Figure 1 is a plot of the effect of the concentration compound II of Example 2 on atrial AV nodal conductance for the A_1 adenosine receptor (-•-) and for the A_2 adenosine receptor (-○-).

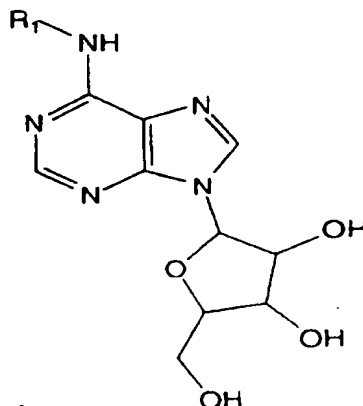
5 Figure 2 is a plot of the effect of the concentration of compound I of Example 2 on atrial AV nodal conductance and specifically on the response of the A_1 adenosine receptor (-•-) and on the response of the A_2 adenosine receptor (-○-).

DESCRIPTION OF THE CURRENT EMBODIMENT

This invention comprises adenosine derivatives which are selective adenosine type 1 receptor agonists. The compositions are optimally substituted as described below.

5

10



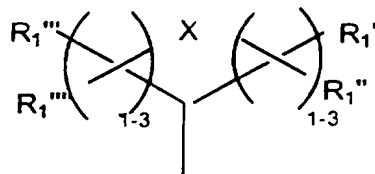
where:

R_1 is a cycloalkyl group, containing 3 to 15 atoms either monocyclic or polycyclic heterocyclic groups, at least one of which is a heteroatom selected from the group consisting of N, O, P, and S-(O)₀₋₂. R_1 , in turn, may optionally be mono or polysubstituted with halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, and cyano. However, R_1 cannot contain an epoxy group.

R_1 is preferably a monocyclic, bicyclic, or tricyclic group containing from 3 to 15 atoms, at least one of which is selected from the group consisting of O or S-(O)₀₋₂ wherein R_1 may be mono or polysubstituted with one or more compounds selected from the group consisting of halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl,

substituted cycloalkyl, nitro, cyano and mixtures thereof.

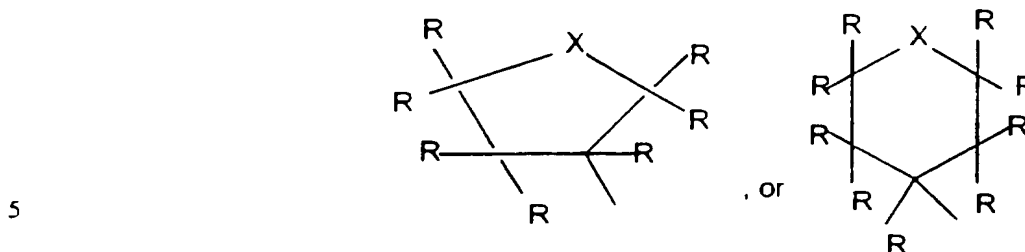
In a more preferred embodiment, R_1 is:



5

wherein R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted
 10 cycloalkyl, nitro, cyano and mixtures thereof and X is O, or S $(-O)_{0.2}$. Preferably, R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group H, lower alkyl, substituted lower alkyl, alkoxy, aryl, and substituted aryl. By "individually selected" it is meant that R_1' , R_1'' , R_1''' , and R_1'''' may each be a different component, each may be the same component, e.g., hydrogen, or some of the components may be the same and some different. It is most
 15 preferred that when R_1 is the composition set forth above, that R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group H, lower alkyl, and substituted lower alkyl. R_1''' and R_1'''' may also be a single oxygen atom.

In an alternative embodiment, R_1 is selected from the group consisting of:



wherein each R may individually selected from the group consisting of H, lower alkyl, and substituted

lower alkyl and wherein X is O, or S $(-O)_{0.2}$. In a most preferred embodiment, R_1 is selected
 10 from the group consisting of 3-tetrahydrofuranyl, 3-tetrahydrothiofuranyl, 4-pyranyl and 4-thiopyranyl.

The following definitions apply to terms as used herein.

The term "halogen" refers to fluorine, bromine, chlorine, and iodine atoms.

The term "oxo" refers to $=O$.

15 The term "hydroxyl" refers to the group $-OH$.

The term "lower alkyl" refers to a cyclic, branched or straight chain, alkyl group of one to ten carbon atoms. This term is further exemplified by such groups as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl, hexyl and the like.

20 The term "substituted lower alkyl" refers to lower alkyl as just described including one or more groups such as hydroxyl, thiol, alkylthiol, halogen, alkoxy, amino, amido, carboxyl, cycloalkyl, substituted cycloalkyl, heterocycle, cycloheteroalkyl, substituted cycloheteroalkyl, acyl, carboxyl, aryl, substituted aryl, aryloxy, hetaryl, substituted hetaryl, aralkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, alkyl cycloheteroalkyl,

and cyano. These groups may be attached to any carbon atom of the lower alkyl moiety.

The term "alkoxy" refers to the group -OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as
5 defined below.

The term "acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl, amino, and the like as defined below.

The term "aryloxy" denotes groups -OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined below.

10 The term "amino" refers to the group $\text{NR}_2\text{R}_2'$, where R_2 and R_2' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein.

The term "carboxyl" denotes the group -C(O)OR, where R may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted
15 hetaryl and the like as defined herein.

The term "aryl" or "Ar" refers to an aromatic carbocyclic group having at least one aromatic ring (e.g., phenyl or biphenyl) or multiple condensed rings in which at least one ring is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl).

The term "substituted aryl" refers to aryl optionally substituted with one or more
20 functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, alkylthio, thiol sulfamido and the like.

The term "heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g., morpholino, pyridyl or furyl) or multiple condensed rings

(e.g., naphthpyridyl, quinoxalyl, quinoliny, indoliziny or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "heteroaryl" or "hetar" refers to a heterocycle in which at least one heterocyclic ring is aromatic.

The term "substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

The term "substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, e.g., halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The compositions of this invention are useful as A₁ receptor agonists for the treatment of coronary electrical disorders such as supraventricular tachycardias, including atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia. The compositions may be administered orally, intravenously, through the epidermis or by any other means known in the art for administering a therapeutic agents.

The method of treatment comprises the administration of an effective quantity of the

chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, age and condition of the patient. These dosage units may be administered one to ten times daily
5 for acute or chronic disorders. No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

If the final compound of this invention contains a basic group, an acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric,
10 hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methane sulfonic. The hydrochloric salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+ , K^+ , Ca^{+2} and NH_4^+ are examples of cations present in pharmaceutically
15 acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

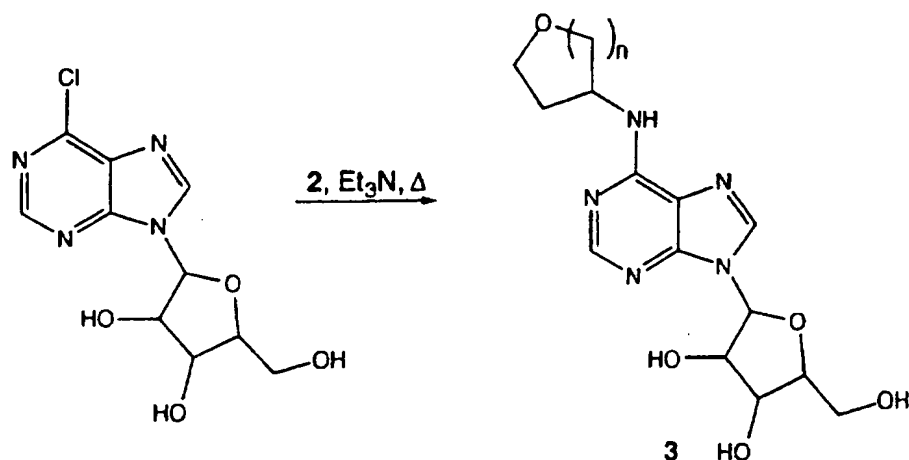
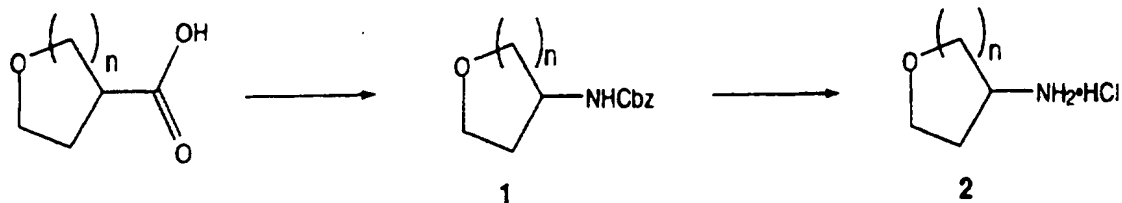
Pharmaceutical compositions including the compounds of this invention, and/or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other
20 pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water and buffered sodium or ammonium acetate solution. Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration. It may

be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this invention. Alternatively, the pharmaceutical compounds may be
5 encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin,
10 acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit. The pharmaceutical dosages are made using conventional techniques such as milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing
15 and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

The Examples which follow serve to illustrate this invention. The Examples are
20 intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention. In the Examples, all temperatures are in degrees Centigrade.

EXAMPLE 1

The compounds of this invention may be prepared by conventional methods of organic chemistry. The reaction sequence outlined below, is a general method, useful for the preparation of compounds of this invention.



5

10

According to this method, oxacycloalkyl carboxylic acid is heated in a mixture of

dioxane, diphenylphosphoryazide and triethylamine for 1 hour. To this mixture is added benzyl alcohol and the reaction is further heated over night to give intermediate compound 1. Compound 1 is dissolved in methanol. Next, concentrated HCl, Pd/C is added and the mixture is placed under hydrogen at 1 atm. The mixture is stirred overnight at room
5 temperature and filtered. The residue is recrystallized to give intermediate compound 2. 6-chloropurine riboside is combined and the mixture is compound 2 dissolved in methanol and treated with triethylamine. The reaction is heated to 80° C for 30 hours. Isolation and purification leads to Compound 3.

EXAMPLE 2

Compounds of this invention prepared according to the method of Example 1 were tested in two functional models specific for adenosine A₁ receptor agonist function. The first was the A₁ receptor mediated inhibition of isoproterenol stimulated cAMP accumulation in DDT cells. The EC₅₀ of each derivative is shown in Table I. Also shown in Table I is the ability of each derivative to stimulate cAMP production in PC12 cells, a function of agonist stimulation of adenosine A₂ receptors. The ratio of the relative potency of each compound in stimulating either an A₁ receptor or an A₂ receptor effect is termed the selectivity of each compound for the A₁ receptor. As can be seen in Table I, each derivative is relatively selective as an A₁ receptor agonist. The use of measuring cAMP metabolism as an assay for adenosine A₁ receptor function has been previously described (Scammells, P., Baker, S., Belardinelli, L., and Olsson, R., 1994, Substituted 1,3-dipropylxanthines as irreversible antagonists of A₁ adenosine receptors. J. Med. Chem 37: 2794-2712, 1994).

Table I

Compound	R	EC ₅₀ (nM) DDT cells	EC ₅₀ (nM) PC12 cells	A ₁ /A ₂	A ₂ /A ₁
I	4-aminopyran	12	970	0.012	80.0
II	(±)-3-aminotetrahydrofuran	13	1400	0.0093	107.6
III	(R)-3-aminotetrahydrofuran	1.08	448	0.0024	414
IV	(1)-caprolactam	161	181	0.889	1.12
V	(S)-3-aminotetrahydrofuran	3.40	7680	0.00044	2258

Compounds were also tested in a whole organ model of A₁ receptor activation with respect to atrial and AV nodal function. In this model, guinea pig hearts are isolated and perfused with saline containing compound while atrial rate and AV nodal conduction time are assessed by electrographic measurement of atrial cycle length and AV intervals, as detailed in Belardinelli, L, Lu, J. Dennis, D. Martens, J, and Shryock J. (1994); The cardiac

effects of a novel A_1 -adenosine receptor agonist in guinea pig isolated heart. J. Pharm. Exp. Therap. 271:1371-1382 (1994). As shown in Figure 1, each derivative was effective in slowing the atrial rate and prolonging the AV nodal conduction time of spontaneously beating hearts in a concentration-dependent manner, demonstrating efficacy as

5 adenosine A_1 receptor agonists in the intact heart.

EXAMPLE 3

Preparation of N-benzyloxycarbonyl-4-aminopyran.

A mixture of 4-pyranilcarboxylic acid (2.28 gm, 20 mmol), diphenylphosphorylazide (4.31 ml, 20 mmol), triethylamine (2.78 ml, 20 mmol) in dioxane
5 (40 ml) was heated in a 100° C oil bath under dry nitrogen for 1 hour. Benzyl alcohol (2.7 ml, 26 mmol) was added, and heating was continued at 100° C for 22 hours. The mixture was cooled, filtered from a white precipitate and concentrated. The residue was dissolved in 2N HCl and extracted twice with EtOAc. The extracts were washed with water, sodium bicarbonate, brine and then dried over MgSO₄, and concentrated to an oil which solidified
10 upon standing. The oil was chromatographed (30% to 60% EtOAc/Hex) to give 1.85 g of a white solid (40%).

Preparation of 4-aminopyran.

N-benzyloxycarbonyl-4-aminopyran (1.85 gm, 7.87 mmol) was dissolved in MeOH (50 ml) along with conc. HCl and Pd-C (10%, 300 mg). The vessel was charged
15 with hydrogen at 1 atm and the mixture was allowed to stir for 18 hours at room temperature. The mixture was filtered through a pad of cclite and concentrated. The residue was co-evaporated twice with MeOH/EtOAc and recrystallized from MeOH/EtOAc to afford 980 mg (91 %) of white needles (mp 228-230° C).

Preparation of 6-(4-aminopyran)-purine riboside.

20 A mixture of 6-chloropurine riboside (0.318 gm, 1.1 mmol), 4-aminopyran-HCl (0.220 mg, 1.6 mmol) and triethylamine (0.385 ml, 2.5 mmol) in methanol (10 ml) was heated to 80° C for 30 hours. The mixture was cooled, concentrated and the residue chromatographed (90:10:1, CH₂Cl₂/MeOH/PrNH₂).

The appropriate fractions were collected and rechromatographed using a chromatotron (2 mm plate, 90: 10: 1, $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{PrNH}_2$) to give an off white foam (0.37 gm, 95%).

EXAMPLE 4

Preparation of N-benzyloxycarbonyl-3-aminotetrahydrofuran.

A mixture of 3-tetrahydrofuroic acid (3.5 gm, 30 mmol), diphenylphosphorylazide (6.82 ml, 32 mmol), triethylamine (5 ml, 36 mmol) in dioxane (35 ml) was stirred at RT for 5 20 min then heated in a 100° C oil bath under dry nitrogen for 2 hours. Benzyl alcohol (4.7 ml, 45 mmol) was added, and continued heating at 100° C for 22 hours. The mixture was cooled, filtered from a white precipitate and concentrated. The residue was dissolved in 2N HCl and extracted twice using EtOAc. The extracts were washed with water, sodium bicarbonate, brine dried over MgSO₄, and then concentrated to an oil which solidifies upon 10 standing. The oil was chromatographed (30% to 60% EtOAc/Hex) to give 3.4 g of an oil (51 %).

Preparation of 3-aminotetrahydrofuran.

N-benzyloxycarbonyl-3-aminotetrahydrofuran (3.4 gm, 15 mmol) was dissolved in MeOH (50 ml) along with conc. HCl and Pd-C (10%, 300 mg). The vessel was 15 charged with hydrogen at 1 atm and the mixture was allowed to stir for 18 hours at room temperature. The mixture was filtered through a pad of celite and concentrated. The residue was co-evaporated two times with MeOH/EtOAc and recrystallized from MeOH/EtOAc to give 1.9 g of a yellow solid.

Preparation of 6-(3-aminotetrahydrofuranyl)purine riboside.

20 A mixture of 6-chloropurine riboside (0.5 gm, 1.74 mmol), 3-aminotetrahydrofuran (0.325 gm, 2.6 mmol) and triethylamine (0.73 ml, 5.22 mmol) in methanol (10 ml) was heated to 80° C for 40 hours. The mixture was cooled, and concentrated. The residue was filtered through a short column of silica gel eluting with 90/10/1 (CH₂Cl₂/MeOH/PrNH₂), the fractions containing the product were combined and concentrated. The residue was

chromatographed on the chromatotron (2 mm plate, 92.5/7.5/1, $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{P}_4\text{NH}_2$). The resulting white solid was recrystallized from MeOH/EtOAc to give 0.27 gm of white crystals (mp 128-130° C).

EXAMPLE 5

Resolution of 3-aminotetrahydrofuran hydrochloride

A mixture of 3-aminotetrahydrofuran hydrochloride (0.5 gm, 4 mmol) and (S)-(+)-10-camphorsulfonyl chloride (1.1 gm, 4.4 mmol) in pyridine (10 ml) was stirred for 4 hours at room temperature and then concentrated. The residue was dissolved in EtOAc and washed with 0.5N HCl, sodium bicarbonate and brine. The organic layer was dried over MgSO_4 , filtered and concentrated to give 1.17 g of a brown oil (97%) which was chromatographed on silica gel (25% to 70% EtOAc/Hex). The white solid obtained was repeatedly recrystallized from acetone and the crystals and supernatant pooled until an enhancement of greater than 90% by ^1H NMR was achieved.

Preparation of 3-(S)-aminotetrahydrofuran hydrochloride.

The sulfonamide (170 mg, 0.56 mmol) was dissolved in conc. HCl/AcOH (2 mL each), stirred for 20 hours at room temperature, washed three times with CH_2Cl_2 (10 ml) and concentrated to dryness to give 75 mg (quant.) of a white solid.

15 Preparation of 6-(3-(S)-aminotetrahydrofuranyl)purine riboside.

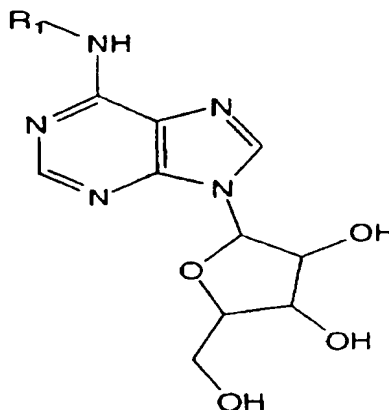
A mixture of 6-chloropurine riboside (30 mg, 0.10 mmol), 3-(S)-aminotetrahydrofuran hydrochloride (19 mg, 0.15 mmol) and triethylamine (45 ml, 0.32 mmol) in methanol (0.5 ml) was heated to 80°C for 18 hours. The mixture was cooled, concentrated and chromatographed with 95/5 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 8 mg (24%) of a white solid.

What we claim is:

1. A composition of matter having the formula:

5

10



wherein R_1 is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 atoms, at least one of which is selected from the group consisting of N, O, P and S-(O)_{0,2} and wherein R_1 does not contain an epoxide group.

15

2. The composition of claim 1 wherein R_1 is mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof.

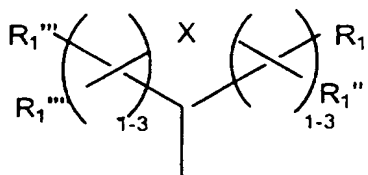
20

3. The composition of matter of claim 1 wherein R_1 is a monocyclic, bicyclic, or tricyclic cycloalkyl group containing from 3 to 15 atoms, at least one of which is selected from the group consisting of O or S-(O)_{0,2}.

4. The composition of claim 3 wherein R_1 is mono or polysubstituted with one or

more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof.

- 5 5. The composition of claim 3 wherein R_1 is:



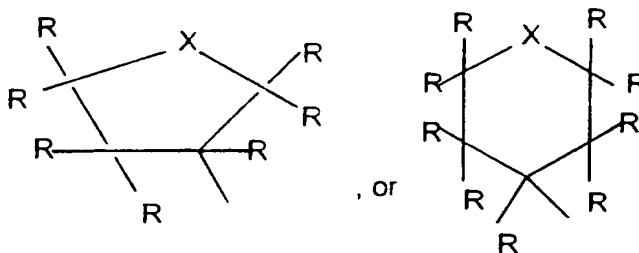
- 10 wherein R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof and X is O, or S $(-O)_{0-2}$.

- 15 6. The composition of claim 5 wherein R_1''' and R_1'''' can be a single oxygen atom.

7. The composition of claim 5 wherein R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group H, lower alkyl, substitute lower alkyl, alkoxy, aryl, and substituted aryl.

- 20 8. The composition of claim 5 wherein R_1' , R_1'' , R_1''' , and R_1'''' are individually selected from the group H, lower alkyl, and substitute lower alkyl.

9. The composition of claim 1 wherein R_1 is selected from the group consisting of:



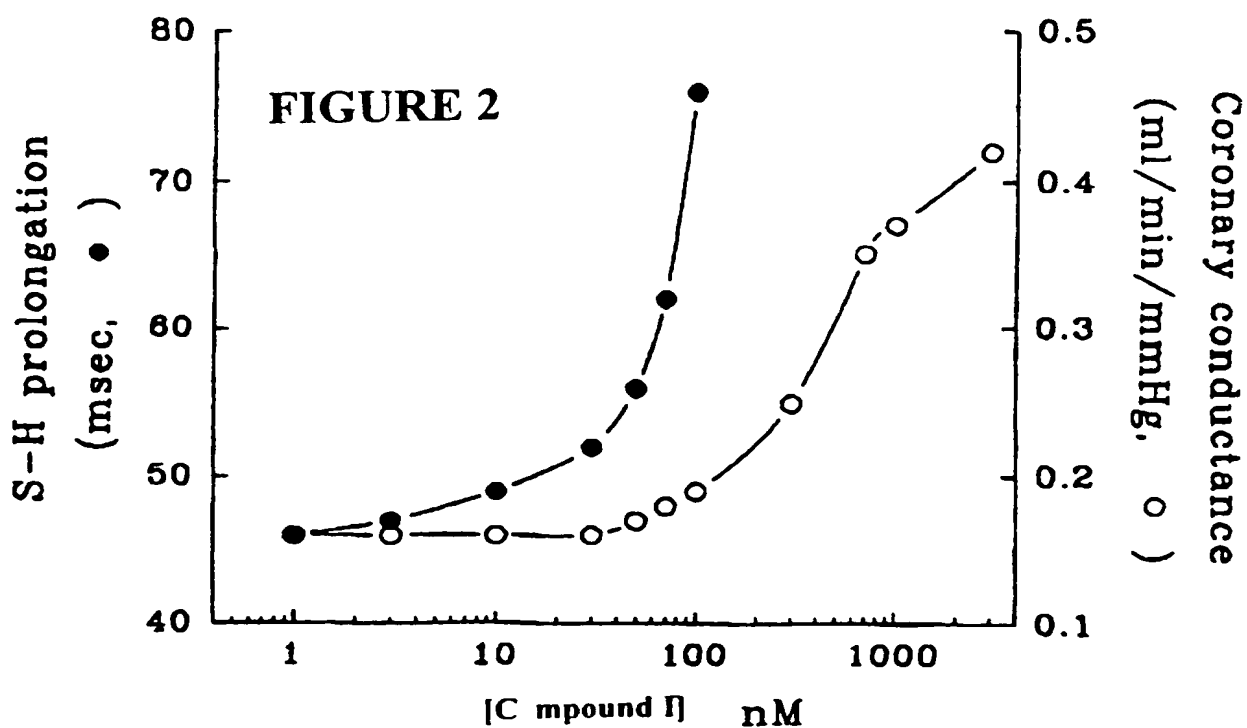
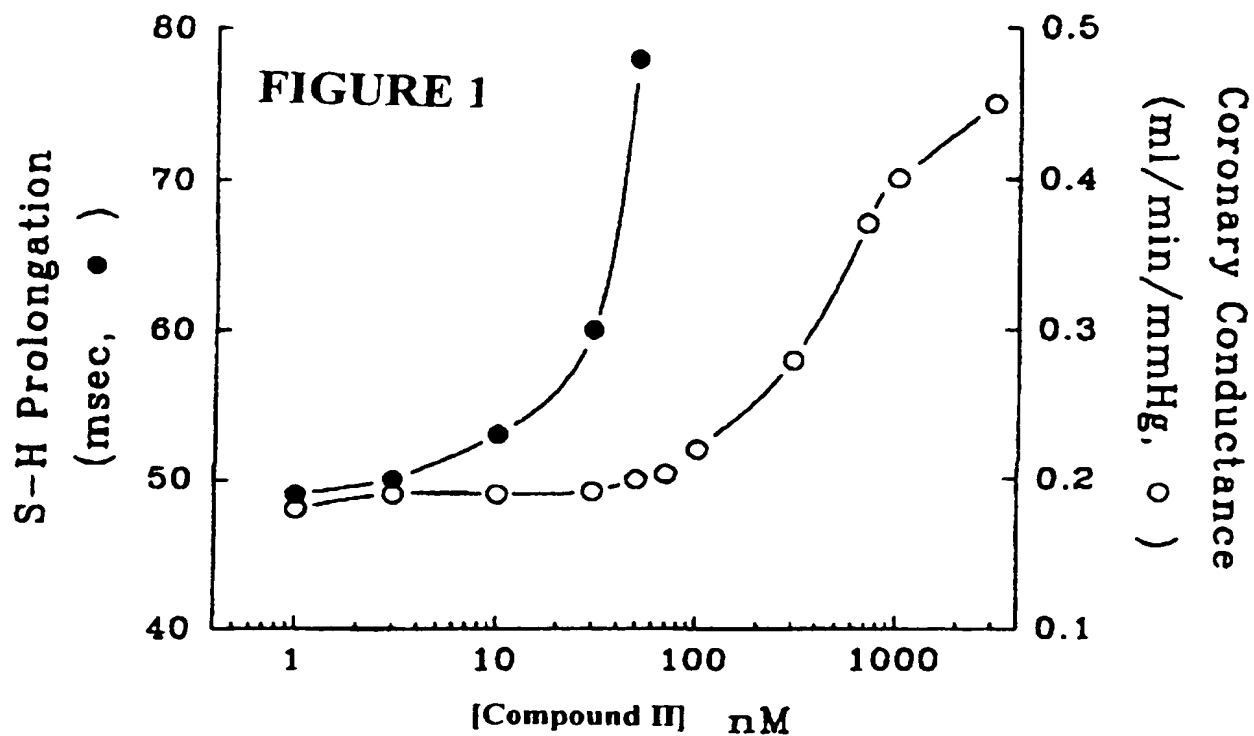
wherein each R may individually selected from the group consisting of H, lower alkyl, and substituted lower alkyl and wherein X is O, or S $(-O)_{0.2}$.

- 10 10. The composition of claim 1 wherein R_1 is selected from the group consisting of 3-tetrahydrofuranyl, 3-tetrahydrothiofuranyl, 4-pyranyl, and 4 thiopyranyl.
11. An adenosine type 1 receptor agonist comprising the composition of claim 1.
12. A method for stimulating coronary activity in a mammal experiencing a coronary electrical disorder that can be treated by stimulating an A_1 hear adenosine receptor
- 15 comprising cell proliferation in mammals comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.
13. The method of claim 12 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.
14. The method of claim 12 wherein the composition is administered to a mammal
- 20 experiencing a coronary electrical disorder selected from the group consisting of supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia.
15. The method of claim 14 wherein the mammal is a human.

16. A pharmaceutical composition of matter comprising the composition of claim 1 and one or more pharmaceutical excipients.

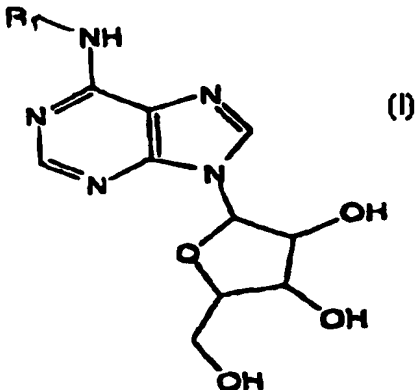
17. The pharmaceutical composition of matter of claim 16 wherein the pharmaceutical composition is in the form of a solution.

5 18. The pharmaceutical composition of matter of claim 16 wherein the pharmaceutical composition is in the form of a tablet.





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ^b : C07H 19/167, A61K 31/70	A3	(11) International Publication Number: WO 98/08855 (43) International Publication Date: 5 March 1998 (05.03.98)
(21) International Application Number: PCT/US97/14724 (22) International Filing Date: 20 August 1997 (20.08.97) (30) Priority Data: 08/702,234 27 August 1996 (27.08.96) US (71) Applicant (for all designated States except US): CV THERAPEUTICS, INC. [US/US]; 3172 Porter Drive, Palo Alto, CA 94304 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LUM, Robert, T. [US/US]; 781 Barron Avenue, Palo Alto, CA 94306 (US). PFISTER, Jurg, R. [US/US]; 1500 Oak Steet, Los Altos, CA 94024 (US). SCHOW, Steven, R. [US/US]; 204 Mendocino Way, Redwood City, CA 94065 (US). WICK, Michael, M. [US/US]; 16 Beresford Road, Chestnut Hill, MA 02146 (US). NELSON, Marek, G. [US/US]; 2690 Park Way, Sunol, CA 95051 (US). SCHREINER, George, F. [US/US]; 12774 Leander Drive, Los Altos Hills, CA 94022 (US). (74) Agent: HUGHES, A., Blair, McDonnell, Boehnen, Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 3 September 1998 (03.09.98)
(54) Title: N ⁶ HETEROCYCLIC SUBSTITUTED ADENOSINE DERIVATIVES		
(57) Abstract <p>A substituted N⁶-oxa, thia, thioxa and azacycloalkyl substituted adenosine derivative of formula (I) and a method for using the composition as an A₁ heart adenosine receptor. In said formula, R₁ is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 atoms, at least one of which is selected from the group consisting of N, O, P and S-(O)₀₋₂ and wherein R₁ does not contain an epoxide group.</p> <div style="text-align: right;">  <p>(I)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CJ	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/14724

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 062 921 A (FUJISAWA PHARMACEUTICAL CO) 20 October 1982 see page 6, test compounds 3-7; page 7, test compounds 3-7 ---	1,2, 11-18
X	EP 0 402 752 A (HOECHST ROUSSEL PHARMA) 19 December 1990 see the whole document ---	1,2,11, 16-18
X	WO 90 09178 A (WHITBY RESEARCH INC) 23 August 1990 see the whole document ---	1,2, 11-18
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

17 December 1997

Date of mailing of the international search report

20.07.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

SCOTT, J

INTERNATIONAL SEARCH REPORT

Inter.: International Application No

PCT/US 97/14724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 121, no. 3, 18 July 1994 Columbus, Ohio, US; abstract no. 26237z, L.J.S.KNUTSEN ET: "The Synthesis and Biochemical Evaluation of new A1 Selective Adenosine Receptor Agonists Containing 6-Hydrazinopurine Moieties." page 18; column 2; XP002050568 see abstract & BIOORG. MED. CHEM. LETTERS, vol. 3, no. 12, 1993, page 2661-6 ---	1,2, 11-15
X	CHEMICAL ABSTRACTS, vol. 105, no. 9, 1 September 1986 Columbus, Ohio, US; abstract no. 72837n, S.ODAWARA ET AL.: "Relaxations of Isolated Rabbit Coronary Artery by Purine Derivatives : A2-Adenosine Receptors." page 88; column 2; XP002050569 see abstract & J. CARDIOVASC. PHARMACOL., vol. 8, no. 3, 1986, pages 567-573, ---	1,2,11
Y	WO 93 08206 A (NOVONORDISK AS) 29 April 1993 see the whole document ---	1,2, 11-18
Y	WO 88 03148 A (WARNER LAMBERT CO) 5 May 1988 see the whole document -----	1,2, 11-18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 14724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 12-15
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See further information

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2, 11-18 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims : 1,2,11-18 partially
Compounds of claim 1 where R1 is a nitrogen containing monocyclic heterocycle, pharmaceutical compositions containing them and their uses
2. Claims : 1,2,11-18 partially
Compounds of claim 1 where R1 is an oxygen containing monocyclic heterocycle, pharmaceutical compositions containing them and their uses
3. Claims : 1,2,11-18 partially
Compounds of claim 1 where R1 is a phosphorous containing monocyclic heterocycle, pharmaceutical compositions containing them and their uses
4. Claims : 1-18 partially
Compounds of claim 1 where R1 is an S-(O)0-2 group containing monocyclic heterocycle, pharmaceutical compositions containing them and their uses
5. Claims : 1-8,11-18 partially
Compounds of claim 1 where R1 is a polycyclic heterocycle. pharmaceutical compositions containing them and their uses

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/14724

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0062921	A	20-10-1982	JP 57171998 A	22-10-1982
			US 4464361 A	07-08-1984

EP 0402752	A	19-12-1990	US 5017578 A	21-05-1991
			AT 127807 T	15-09-1995
			AU 636351 B	29-04-1993
			AU 5691990 A	13-12-1990
			CA 2018563 A	09-12-1990
			CN 1047866 A,B	19-12-1990
			DE 69022294 D	19-10-1995
			DE 69022294 T	14-03-1996
			DK 402752 T	15-01-1996
			ES 2078267 T	16-12-1995
			GR 3017743 T	31-01-1996
			HU 207320 B	29-03-1993
			IE 68433 B	12-06-1996
			IL 94665 A	24-06-1994
			JP 1967647 C	18-09-1995
			JP 3024080 A	01-02-1991
			JP 6102663 B	14-12-1994
			MX 21088 A	01-11-1993
			PT 94297 A,B	08-02-1991
			US 5155098 A	13-10-1992

WO 9009178	A	23-08-1990	AU 626983 B	13-08-1992
			AU 4941490 A	05-09-1990
			EP 0457773 A	27-11-1991
			US 5565566 A	15-10-1996

WO 9308206	A	29-04-1993	AU 657374 B	09-03-1995
			AU 2916092 A	21-05-1993
			CA 2121844 A	29-04-1993
			EP 0609375 A	10-08-1994
			FI 941876 A	22-06-1994
			IL 103513 A	12-09-1996
			JP 7500586 T	19-01-1995
			NO 941477 A	23-06-1994
			NZ 244875 A	27-04-1995
			US 5578582 A	26-11-1996
			US 5432164 A	11-07-1995

THIS PAGE BLANK (USPTO)